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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/784,163	02/24/2004	David Tacha	247232US23	2363

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EXAMINER	
GRUN, JAMES LESLIE	
ART UNIT	PAPER NUMBER
1641	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	03/23/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 03/23/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/784,163	TACHA, DAVID	
	Examiner	Art Unit	
	James L. Grun	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *81-103* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *81-103* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/24/04; 8/23/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *IDS 9/12/06*.

Applicant's election with traverse of Group VI, claims 81-92, in the paper filed 23 August 2006 is acknowledged. Applicant's further election with traverse of a species in the paper filed 21 December 2006 is acknowledged. The traversals are on the ground(s) that adequate reasons have not been provided to support patentable distinctness between the groups or species, or to support a serious burden on the examiner. These are not found persuasive for the reasons of record because the explanations of different designs, modes of operation, functions, effects, scope, classifications, and fields of search made in the restriction requirement of record are sufficient to provide a *prima facie* showing of a serious burden upon the examiner.

The requirement is still deemed proper and is therefore made FINAL.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 81-103 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 81 and claims dependent thereupon, "the formation" lacks antecedent basis. It is not clear what applicant intends as encompassed within the metes and bounds of the method because it is not clear which two antigen-antibody complexes are sufficient for the detecting step, e.g. the detection of a complex of the first secondary antibody bound to the first primary antibody bound to antigen in sample meets the limitation as claimed because the first primary antibody is antigen for the first secondary antibody. The claims are confusing because, for the reasons set forth immediately above, the preamble recites detecting two or more antigens in

sample but the body of the claims do not recite a step relating detecting formation of at least two antigen-antibody complexes to detecting two or more antigens in sample.

In claim 87 and claims dependent thereupon, "the formation" lacks antecedent basis. It is not clear what applicant intends as encompassed within the metes and bounds of the method because it is not clear which two antigen-antibody complexes are sufficient for the detecting step, e.g. the detection of a complex of the first secondary antibody bound to the first primary antibody bound to antigen in sample meets the limitation as claimed because the first primary antibody is antigen for the first secondary antibody. The claims are confusing because, for the reasons set forth immediately above, the preamble recites detecting two or more antigens in sample but the body of the claims do not recite a step relating detecting formation of at least two antigen-antibody complexes to detecting two or more antigens in sample.

In claim 93 and claims dependent thereupon, improper Markush language is used to claim the members of the group. The alternatives "selected from...or" or "selected from the group consisting of...and" are acceptable.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> (c) Subject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 81-103 are rejected under 35 U.S.C. § 103(a) as being unpatentable over C. M. van der Loos (1999) in view of applicant's admissions and either of Myers et al. (J. Surg. Pathol. 1: 105, 1995) or Hasui et al. (J. Histochem. Cytochem. 51: 1169, 2003).

The handbook of C. M. van der Loos teaches conventional methods and reagents for immunoenzyme multiple staining protocols. In particular, the reference teaches indirect/indirect simultaneous double staining using cocktails of primary antibodies from different animal species or of different immunoglobulin isotypes and cocktails of labeled secondary antibodies specific for the primary antibodies (see pages 14, 15, 33-36, and 82-85). Labelling with horseradish peroxidase and alkaline phosphatase is taught, including the use of polymeric conjugates of secondary antibodies and label (see e.g. page 4 or 15). Combinations of staining protocols to perform staining of more than two antigens in a single sample are taught, including the use of combinations involving simultaneous double staining with sequential double staining (e.g. page 63). Although the reference teaches various multiple antigens detected simultaneously (see e.g. pages 16-32 and 103-112), the reference does not teach detection of combinations of antigens as instantly claimed.

Either of Myers et al. (1995) or Hasui et al. (2003) teach automation of multiple staining protocols. Myers et al. in particular teach the combination of CD-20 and Ki-67 for simultaneous determination (see e.g. Fig. 2 and page 110).

Applicant admits that the detection of the combination of P504S, HMWCK and p63 is routine in the art (see page 2).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have selected from the alternatives taught by the handbook of C. M. van

der Loos to perform immunoenzyme multiple staining protocols for any desired pair or multiple of antigens, as taught in for example in C. M. van der Loos, Myers et al., or applicant's admissions, in view of the direct suggestions in the reference to do so motivated by the expectation that the conventional reagents and methods would successfully perform as conventionally known in the multiple staining protocols. It would have been obvious to have generated and used monoclonal antibodies in the protocols in order to provide a potentially unlimited source of homogeneous reagent. Automation of multiple staining protocols is well known in the art, as taught in either of Myers et al. (1995) or Hasui et al. (2003), and it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have automated the protocols taught by the handbook of C. M. van der Loos, as modified, for the benefits of standardization, accuracy, and consistency taught in either of Myers et al. (1995) or Hasui et al. (2003).

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claims 81, 87, 93, and 100 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mason et al. (J. Can. Res. Clin. Oncol. 101: 13, 1981) in view of Shi et al. (Appl. Immunohistochem. Mol. Morph. 7: 201, 1999).

Mason et al. teach simultaneous double immunoenzymatic labeling using cocktails of primary antibodies from different animal species and cocktails of labeled secondary antibodies specific for the primary antibodies. Labelling with horseradish peroxidase and alkaline phosphatase is taught. Simultaneous detection of κ and λ chains is specifically exemplified (see

e.g. Figs. 2 or 3). Mason et al. suggest conjugates of enzymes with secondary antibodies as a substitute for the peroxidase-anti-peroxidase complexes used as labels in the exemplified methods (see page 20). In contrast to the invention as instantly claimed, the reference does not teach coupling secondary antibodies to polyenzyme moieties.

Shi et al. teach polymerized enzyme-antibody conjugates for immunohistochemistry as a substitute for other labels such as peroxidase-anti-peroxidase complexes.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have substituted the conjugates of Shi et al. for the peroxidase-anti-peroxidase complexes used in Mason et al. in view of the direct suggestions of both Mason et al. and Shi et al. to make the substitution.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Damaj et al. (US 2002/0173053) teach simultaneous antigen detection by immunohistochemistry. Mixtures of different antibody populations, specific for different markers to be determined, each conjugated to a different enzyme, e.g. horseradish peroxidase and alkaline phosphatase (see [0027], [0036], [0046] and claim 7), were made in blocking buffer (see [0027]). Blocking buffer comprised borate buffer, 0.05% TWEEN 20, 0.25% bovine serum albumin, and 0.05% sodium azide. Substrates for the different enzymes were added sequentially

([0047]). The reference teaches alternative labeling known to the art ([0006]). The reagents are provided in a kit ([0013]).

Tidman et al. (Clin. Exp. Immunol. 45: 457, 1981) teach double staining with mixtures of antigen-specific primary antibodies elicited in different animal species or of different immunoglobulin subclasses followed by mixtures of secondary labeled antibodies specific for the primary antibodies. Although the reference specifically exemplifies fluorescent labels, it teaches alternative labels such as combinations of peroxidase- and alkaline-phosphatase-conjugated secondary antibodies (see page 465). The antibody diluent was not specifically taught.

Henning et al. (US 2002/0106685) teach simultaneous antigen detection by immunocytochemistry. The reference teaches an antibody diluent formulation of phosphate-buffered saline, having 6 mM phosphate (KH_2PO_4/Na_2HPO_4), 3mM KCl, and 137 mM NaCl, and 5% fetal calf serum (see [0036]).

Chien et al. (US 6,537,745) teach that substitution of reagents in a buffer with reagents performing essentially the same function is well known in the art, such as substitution of borate with phosphate buffering agents, or substitution of gelatin with albumin or other blocking agents (cols. 3, 6-7, 9), or substitution of a single blocking agent with a mixture thereof (see cols. 6-7).

Nakane (J. Histochem. Cytochem. 16: 557, 1968) teaches elution with buffered or unbuffered hydrochloric acid for immunohistochemical staining of multiple antigens.

Hasui et al. (J. Histochem. Cytochem. 51: 1169, 2003) teach elution with buffered hydrochloric acid for immunohistochemical staining of multiple antigens.

Loor et al. (US 4,690,890) teach immunoassays, for the detection of multiple antigens, which may use different enzyme labels on antigen-specific antibodies in a mixture to detect the different antigens (col. 6-8). The reference teaches that immunoassays are typically performed at pH 6-9 (col. 8). The reference teaches antibody diluents having 0.05M Tris, 0.05% preservative, 1.0% BSA, and 100 mM NaCl (col. 15), or 0.05M Tris, 0.05% preservative, 5.0% BSA, and 100 mM NaCl (col. 16).

Philo et al. (US 5,108,896) teach immunoassays, for the detection of multiple antigens, which may use different labels on antigen-specific antibodies in a mixture to simultaneously detect the different antigens. The antibody mixtures were diluted in a buffer comprising 0.1M Tris/HCl, 0.2% sodium azide, 0.5% BSA, serum, and 100 mM NaCl (col. 11).

Diamandis et al. (US 5,089,423) teach antibody diluents of various formulations, e.g.: 0.01M Tris, 0.01% sodium azide, 1% BSA, and 0.01% thimerosal (col. 11); 0.05M Tris, 0.05% sodium azide, 0.5% BSA, 0.01% TWEEN, 150 mM NaCl (col. 14); or, 0.05M Tris, 0.05% sodium azide, 1.0% BSA, 150 mM NaCl (col. 20).

Krajewski et al. (Anal. Biochem. 236: 221, 1996) teach an antibody diluent for detection of multiple antigens comprising 0.01M Tris, 2% BSA, 0.1% serum, 5% skim milk, 0.05-0.1% TWEEN 20, 0.01% sodium azide or 0.01% thimerosal, and 150 mM NaCl. The reference teaches a formulation of phosphate-buffered saline having 41.5 mM phosphate (K_2HPO_4/NaH_2PO_4) and 120 mM NaCl.

Boscato et al. (Clin Chem. 32 : 1491, 1986) teach a phosphate-buffered saline having 10 mM phosphate (KH_2PO_4/Na_2HPO_4), 0.1% sodium azide, 10 mM EDTA, and 150 mM NaCl, also containing 0.1 % serum albumin for dilution of antibody.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, SPE, can be contacted at (571) 272-0823.

The phone number for official facsimile transmitted communications to TC 1600, Group 1640, is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JLG

James L. Grun, Ph.D.
March 15, 2007

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